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Review Article

Endocannabinoidome and its role in neurological disorders-A comprehensive update of existing literature

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Abstract

Medical benefits of cannabis and related compounds is widely known. Discovery of psychotropic plant cannabinoid Δ9-tetrahydrocannabinol have urged researchers to study more about the cannabinoid system and related therapeutics in the field of neurology and medicine. Where activation of cannabinoid receptor type 1 (CB1R) yielded in unwanted and serious side effects, discovery of cannabinoid receptor type 2 (CB2R) and its ligands gave a new hope. Till now there is limited success in this field because of complex expanded endocannabinoid system comprising of receptors, ligands and enzymes. In this review we will update about the role of endocannabinoidome relevant to neurological disorders.

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Introduction

Anecdotal evidence and recent case reports talked about the therapeutic effect of cannabis sativa [1]. First cannabis derived compound, dronabinol was approved in clinical practice in late 20th century. In 2011, it was approved for treating spasticity in multiple sclerosis (MS) [2-4]. Two specific cannabinoids discovered in the 1960s were Δ9-tetrahydrocannabinol (THC) and the non-euphoric cannabidiol (CBD) [5]. However, mechanism of action of THC, a psychotropic component of marijuana gave us the insight and discovery of the receptors in 1990s [6,7], consequently, of endogenous ligands of these receptors, endocannabinoid [8].

Endocannabinoids and cannabinoid receptors are signaling molecules which are mainly pleiotropic in nature. They are responsible in maintaining homeostatic milieu in central and peripheral nervous system after a significant pathological insult. This ultimately leads to treatment opportunities of complicated neurological disorders as well as diseases of the peripheral organ systems [9-13]. Study in animal models showed that this signaling system is altered in neurological diseases [14]. Nabiximols (Sativex®), a combination of THC and CBD, was an important breakthrough drug for MS patients in treating pain and moderate to severe spasticity [3].

Endocannabinoid system consists of CB1, CB2, two endocannabinoids especially 2-arachidonoylglycerol (2-AG) and anandamide, and anabolic and catabolic enzymes of the endocannabinoid family. Endocannabinoid signaling is related to multiple neurological diseases. It participates in development of brain, release of neurotransmitters, neuronal plasticity, and cytokine release from microglial cells thereby maintaining homeostasis at a cellular level [15].

A new expanded signaling system, called as endocannabinoidome was coined because endocannabinoids activated different receptors and their anabolic/biosynthetic and catabolic pathways were often shared with other mediators. A lot of interest has been generated recently in research community in decoding the role of endocannabinoidome, anabolic/catabolic enzymes, allosteric modulators or inhibitors in terms of brain and especially neuronal pathology [16].

THC was considered to be a psychotropic agent but many unique compounds are developed now and almost none are psychotropic. Central and peripheral targets have been identified and being studied [17]. CBD modulates the activity of several proteins whereas THC induces psycho-activity thereby giving CBD an edge [18,19].

CB1 receptor is found in both peripheral and central nervous system. CB2 is mainly responsible for psychoactive

properties of THC, active agent in medical cannabis and most importantly in determining endocannabinoid-mediated presynaptic-inhibition efficacy. Both of them are G protein-coupled receptor (GPCR) based [6,7].

Inhibition of fatty acid amide hydrolase (FAAH) controls degradation of endocannabinoid. The mechanism is complex and associated with activation of transient receptor potential cation channel subfamily V member 1 (TRPV1), G protein-coupled receptor 119 (GPCR 119/GPR119), orphan G protein-coupled receptor 55 (GPR55), and peroxisome proliferator-activated receptor-alpha (PPARα) [14].

TRPV1, GPR 55/119, and PPARα often functions opposite to those of cannabinoid receptors [20-23]. 2-AG is a precursor of arachidonic acid and pro-inflammatory prostanoids, so beneficial effects of monoacylglycerol lipase (MAGL) inhibitors, particularly those seen in experimental models of Alzheimer's disease (AD) and Parkinson's disease (PD) might be mediated by inhibition of prostanoid receptor signaling [24,25].

The super complex signaling system comprises of endocannabinoid-related molecules extending to several long- chain N- acyl-amides mainly N- acyl-taurines, serotonin, dopamine, and fatty acid primary amide [26].

The most likely location of CB1is presynaptic in both excitatory and inhibitory neurons [27,28]. CB1 controls vesicular release of gamma aminobutyric acid (GABA) or glutamate by inhibiting voltage-gated Ca2+ channels [27]. Endocannabinoids, particularly 2-AG, are inhibitory retrograde neuromodulators [29]. Slow self-inhibition of neocortical interneurons is mediated by postsynaptic CB1 receptors [30].

A small proportion of postsynaptic CB1 is located in the external membrane of mitochondria [31], where it inhibits electron transport and the respiratory chain, thereby affecting brain metabolism and memory formation [32]. Activation of CB1 also stimulates proliferation of adult progenitor stem cells and their differentiation into neurons or astrocytes [33], a role that could be relevant to neurodegenerative disorders.

CB2 is expressed in microglia in diseases such as amyotrophic lateral sclerosis (ALS), MS, AD as evident from pathological studies of human brain samples [34]. CB2 activation also stimulates adult neurogenesis [35], and plays an active role in regulating blood–brain barrier (BBB) permeability [36]. CB2 is expressed at very low levels in healthy neurons and that their activation has the opposite effects to CB1 activation [37,38]. One study has suggested that activation of postsynaptic CB2 reduces neuronal excitability in the CA3 and CA2 regions of the hippocampus through functional coupling with the sodium bicarbonate transporter [39].

The most studied of the receptors involved in the wider endocannabinoidome are TRPV1, peroxisome proliferator-activated receptor -gamma (PPARγ) and PPARα, although some work has addressed the role of two orphan GPCRs, GPR55 and GPR18. TRPV1 is found in glutamatergic, GABAergic terminals, and neuronal soma in the hippocampus and cerebellum [40,41].

PPARγ and PPARα are expressed in brain cells like microglia and astrocytes and even neurons. They exhibit neuroprotective effects and inhibit neuroinflammation during any acute or chronic insults in the form of traumatic brain injury, ischemic insult, neurodegenerative diseases like AD and MS [42].

The role of GPR 55 is controversial but evidence suggests that its activation stimulates excitatory hippocampal neurons [43] and only little information is available of GPR 18. However, presence of GPR 18 in microglia has neuroinflammatory function [44].

Neurological disorders involved with endocannabinoidome system

Parkinson's Disease (PD): TRPV1 and CB1R are responsible for CBD-induced analgesic effect by increasing endogenous anandamide levels. Reduction of parkinsonism-induced nociceptive threshold can be achieved by CBD [45].

Palmitoylethanolamide (PEA) is a nutraceutical endocannabinoid found in egg yolks. It is responsible for targeting non classical cannabinoid receptors and shows no excitatory modulation of CB1 and CB2. Classical receptors of cannabinoid system are only activated by entourage effect [46]. In a mouse-model of PD, PEA restored tyrosine hydroxylase activity in the SNPc, thereby improving dopamine neurotransmission [198,199]

In MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced PD model intraperitoneal PEA injections, maintained expression of tyrosine hydroxylase activity, prevented parkinsonian like behaviors, and had a blunted effect on upregulation of a-synuclein [200]. Addition of ultramicronized PEA to PD patients already receiving levodopa therapy significantly reduced most of the motor and non-motor symptoms [50].

Another study reported cannabinoid receptor antagonist (CBR), SR141716, was responsible for almost full neuroprotection in CBR-expressing cells even when a selective agonist, arachidonyl-2'-chloroethylamide (ACEA), was present. However, in cells expressing CB/GPR55 heteromeric complex, SR141716 was not found to be effective. In addition, an agonist of GPR55, CID1792197, did not enhance neuroprotection in GPR55-expressing cells [47].

In an exploratory, double- blind trial of CBD in patients with PD, the highest dose tested (300 mg daily) improved quality of life [48]. In another pilot study, both THC and

nabilone, a synthetic analogue of THC, reduced levodopa-induced dyskinesia in PD [49]. A recent study found medical marijuana to be effective in alleviating motor symptoms and non-motor symptoms mainly reducing sleep disturbances and pain [201].

Alzheimer's Disease (AD): Severity of agitation may be associated with oxidative stress and neuroinflammation, while nabilone may have anti-inflammatory effects [51]. Heteromer-specific feature suggests that adenosine receptor antagonists would potentiate, via microglia, the neuroprotective action of endocannabinoids with implications for AD therapy [52].

Montanari, et al. in their study evaluated the role of unique 2-arylbenzofuran derivatives towards cannabinoid receptors and cholinesterases. Both of them had neuroprotective and immunomodulatory properties in treatment of AD [53].

Novel insight into the network mechanisms underlying cognitive decline in AD and suggest TRPV1 activation as a novel therapeutic target [54]. Link between the endocannabinoid system and interleukin-1β in the context of AD is also reported [55]. Night-time agitation, eating behavior and aggressiveness, have yielded positive results [56].

Takkinen and colleagues used inverse agonist for CB1R, [18 F] FMPEP-d 2 and PET (Positron Emission Tomography) imaging in a mouse model of AD. They showed genotype- and age-dependent impairments in the availability of CB1R [57]. Beneficial effect of CB2-deficiency in APP transgenic mice. CB2 appears to be part of a protective system that may be detrimental when engaged continuously [58]. CB1R desensitization may be a plausible strategy to improve behavior alterations associated with genetic risk factors for developing AD [59].

THC and nabilone have been tested in controlled clinical trials for the treatment of anxiety, agitation, and depression in AD individuals. THC was found to be ineffective in controlled clinical trials against neuropsychiatric symptoms. However, there was some beneficial effects on gait and balance. Nabilone reduced the severity of agitation [60-63].

Huntington's Disease (HD): Studies have found reduced expression of CB1R in the striatum in HD patients and animal models [202,203]. Endocanabinoid signaling have a significant role in maintaining plasticity within striatum and at the corticostriatal synapse, thereby controlling goal-oriented behaviour [64,204]. Positive allosteric modulation of the CB1R reduces signs and symptoms of HD in the R6/2 mouse model [65].

A recent study involving a Q175 mouse model of HD reported rectification of motivational and dopaminergic deficits once degradation of endocannabinoid is inhibited. Neuropsychiatric symptoms of HD may benefit from CBR based therapies [66].

Recently, a research focused on several methods to quantify cell signaling and GPCR receptor ligand bias characterization of drugs that target the endocannabinoid receptors in HD [67]. Sepers, et al. in their study with a mouse model of HD have showed anandamide exhibiting a selective deficit in synaptic plasticity over 2-AG [68].

In humans with HD, FAAH activity is decreased and, consequently, anandamide levels are increased in lymphocytes [69]. A trial with 26 patients with HD, nabiximols was well tolerated but did not improve disease outcome over time [70], although in a subsequent study of seven patients with early-onset HD, it reduced dystonia [71].

CBD has been tested in 15 patients with HD, but no therapeutic effect was seen, even with a high dose (700 mg daily) [72]. Nabilone has also been tested for the treatment of motor symptoms in patients with HD, with contrasting results [73-76].

Traumatic Brain Injury (TBI): Mild TBI (mTBI) induces a strain-specific CB1-dependent bone anabolic response in the skull, probably mediated by anandamide, but seemingly unrelated to inflammation [77]. Changes in the CNS lipidome associated with mTBI likely play a role in headache and in long-term neurodegenerative effects of repeated mTBI [78]. Boosting endocannabinoid tone post-TBI may represent a viable therapeutic strategy for TBI-related psychiatric comorbidities such as alcohol use disorder and anxiety [79].

AM281, a CB1 receptor antagonist, reversed the TBI-reduced N-Methyl-D-aspartate (NMDA) receptor subunits NR2B in the hippocampus and ameliorate the spatial learning and memory impairment at 7d post-TBI, suggesting CB1 receptor is involved in the TBI-induced hippocampal-dependent spatial learning and memory impairment [80].

Post head injury in animal models, partial recovery of corticospinal tract, inhibition of tumor necrosis factor-α production in vivo, increased synaptic plasticity and neuro behavioral recovery was seen in CB2 agonists [81].

In ischemic brain insult post-TBI, cannabinoid receptor signaling partially mediates protective effects of the MAGL inhibitor. TBI can cause neuroinflammation and cerebral edema caused by BBB dysfunction. MAGL inhibitors can serve as potential therapeutics [82]. Neuroinflammation after TBI can be reduced by selective activation of CB2R via alternative macrophage polarization [83].

In a mouse model of TBI, levels of 2-AG were increased between 1 h and 24 h after injury in the same ipsilateral hemisphere. In the same model, administration of 2-AG protected the BBB, reduced inflammation and oedema and improved clinical recovery via CB1-mediated mechanisms [84,85].

Inhibition of endocannabinoid degradation by blocking FAAH, MAGL or α/β-hydrolase domain-containing 6 (ABHD6) reduced neurodegeneration and inflammation, protected BBB integrity and improved motor impairments, memory deficits and anxiety behavior in different TBI models [86,87].

In mouse models, PEA and N-arachidonoyl-l-serine had beneficial effects in TBI. Reduction of gliosis, cerebral edema, and behavioral deficits was seen with enhanced neurogenesis [88,89].

In several studies in experimental TBI, dexanabinol (also known as HU-211) - an enantiomer of the ultra- potent synthetic CB1 and CB2 ligand HU-210 that is inactive at cannabinoid receptors - exhibited potent neuroprotective activity, probably by inhibiting the NMDA receptor but was never bought to clinical practice because results were negative in phase III trial [90,91].

Seizure and epilepsy: Increase in anandamide levels in brain reduces hyperexcitability. Inhibitors of anandamide hydrolysis may help in reducing convulsions [92]. Cannabidiol has shown and anti-inflammatory and anti-epileptic properties, and it shows promise for epilepsy treatment [93]. Reduced CB2R activity is associated with increased seizure susceptibility [94]. Various models of temporal lobe epilepsy, an agonist of CB1 and CB2 had antiepileptogenic effects [95-97]. CB1 and CB2 blockade had pro- epileptogenic effects [98,99].

Anandamide and 2-AG are released after neuronal hyperexcitability to counteract glutamate excitotoxicity during seizures [100]. FAAH inhibitors protected against seizures induced by pentylenetetrazole or kainic acid [101,102]. CBD had anti- convulsant effects in the pilocarpine model of temporal lobe epilepsy via GPR55 antagonism and TRPV1 desensitization [5,103-104]. It also rescued morphological anomalies in interneurons induced by epilepsy [105].

Two double- blind, placebo- controlled phase III trials have shown CBD to be effective in controlling seizures in Lennox-Gastaut syndrome and Dravet syndrome [19,106]. CBD is also used in rare epileptic disorders including Doose syndrome, Cyclin Dependent Kinase Like 5 (CDKL5) deficiency disorder, Dup15q syndrome, Aicardi syndrome, and treatment-resistant pediatric epilepsies [107,108].

Tourette's Syndrome (TS): THC has proved effective in Tourette syndrome in multiple studies [109-112]. ABX-1431 is an experimental drug that was well-tolerated and found to be safe in phase 1 clinical studies. Data indicates that it has the potential to treat symptoms of adult patients with Tourette's [113]. Improvement in motor and vocal tics was seen with intake of Sativex in two patients [193]. Very limited evidence for THC's role in symptomatic management of TS is only known from some small clinical trials [194].

A recently conducted double blind randomized clinical trial with 96 adult patients showed treatment with the cannabis extract nabiximols is superior to placebo in patients with chronic tic disorders (TS or chronic motor tic disorder) [195].

A recent polish study has shown C allele of rs2023239 polymorphism of the CNR1 gene is a risk factor of TS in Polish population. This unique variant can be possibly associated with abnormal endocannabinoid transmission, a known cause of TS [196]. Cannabis-based medicine might be safe in tics and adults with TS. THC-rich cannabis, dronabinol and nabiximols all can be tried according to preference. Entourage effect might be seen with nabiximols and dronabinol [197].

Stroke and neonatal ischemia: Stimulation with PEA or 2-AG did not change the expression of PPARα but distribution was altered. Co-application of PEA and 2-AG did not provide neuroprotection rather abolished activity was seen. Both exerted opposite effects on function and morphology of microglial cells. This might be because of contrary polarization of microglial cells [114].

Cannabidiol is a publicly available cannabinoid. It does not bind to CB1R and CB2R but neuroprotective properties are observed in stroke [115]. Post ischemic stroke, attenuation of astrocytic scar formation and improvement of motor function can be seen with oleoylethanolamide (OEA). OEA inhibits glial activation via moudulating PPARα [116].

OEA-SPC NPs is a novel neuroprotective nanoformation was found to have neuroprotective effect in vivo. Reduction in infarct volume and cerebral edema was also observed. OEA-SPC NPs was also shown to inhibit the inflammation of reperfusion to a very slight level [117].

In the early pro-inflammatory phase after CNS injury, activation of CB2R can be protective. This activation inhibits neuro-inflammation and, thereby attenuates severity of CNS injury-induced immunodepression (CIDS). However, in later phases inhibition of CB2R can restore immune function, which may be a promising pharmacological strategy [118].

WIN 55212-2 is a potent cannabinoid receptor agonist and a potent analgesic. In permanent and transient middle cerebral artery occlusion models of anoxic stroke, reduced brain tissues damage was observed. Maturation of oligodendroglia and increased oligodendrocyte progenitor cells (OPC) proliferation was seen with WIN 55212-2 [119].

CBD was reported to reduce infarct size in a permanent unilateral middle cerebral artery occlusion. CBD has antagonist like activity towards sigma 1 receptor thereby reducing the negative effects N-methyl-D-aspartate receptor (NMDAR) over activity [120].

Several preclinical models of neonatal hypoxia and ischemic damage improved with CBD derived molecules [121].

Neonatal anoxia-ischemia was shown to be associated with decreased locomotory and impairment of spatial memory. PEA decreased astrogliosis and neuroinflammation [122].

In acute stroke activation of CB1R decreases cerebral edema, reduces infarcted tissue volume, and maintains BBB integrity. Activation of CB1R induces hypothermia like state which is neuroprotective, effects that are all usually reversed by CB1 antagonists [123-125]. Stroke severity was increased in CB1 knockout mice [126].

One study has suggested that CB1 antagonists could be protective in transient or permanent cerebral artery occlusion [127]. In mice with middle cerebral artery occlusion, CB2 activation reduced infarct volume and improved neurological outcome and cerebral microcirculatory function [128,129].

After hypoxia induced ischemia in newborn pigs, CBD reduced cerebral edema and convulsive seizures [130], and brain damage was reversed after 72 h from treatment [131], CBD also has a neuroprotective effect that is partly mediated by adenosine 2A receptors [132].

Nabiximols is currently being tested as an add- on therapy for post- stroke spasticity [133]. Previously, PEA with luteolin was tested in patients with stroke during rehabilitation. It improved pain, spasticity, cognitive dysfunction, and bought independence in daily living activities [134].

Amyotrophic Lateral Sclerosis (ALS): CBRs are elevated in the motor cortex of motor neuron disease (MND) patients associated with the reactive gliosis. This phenomenon is previous to neuronal losses. CB receptors in cortical and spinal motor neurons. These observations support that targeting this receptor may serve for developing neuroprotective therapies in MNDs [135].

Elevating 2-AG levels by MAGL inhibition is a therapeutic target in ALS and demonstrate that the endocannabinoid defense mechanisms [136]. Marked upregulation of CB receptors in the spinal cord in canine degenerative myelopathy (DM), which is concentrated in activated astrocytes was observed [137]. CB1 unlikely to be beneficial as in superoxide dismutase 1 (SOD1) model as it was downregulated [138].

CB2 was upregulated in the spinal cord of SOD1 mice and in activated microglia in the spine of TAR- DNA binding protein 43 (TDP43) mutant mice [139,140]. CB2 is known to be upregulated in post- mortem spinal cord and primary motor cortex samples in patients with ALS. Furthermore, a selective CB2 agonist slowed disease progression in SOD1 mice, and these findings together suggest that CB2 has a protective role in ALS [139,141].

In SOD1 mice, anandamide and 2-AG concentrations are increased in the lumbar spinal cord [142]. Genetic knockout of FAAH in SOD1 mice prevented development of symptoms without prolonging survival [143]. Administration of an MAGL inhibitor delayed disease onset, slowed progression and increased survival [144], suggesting that the increases in anandamide and, in particular, 2-AG are neuroprotective.

In human gingiva- derived mesenchymal stromal cells, CBD modulated expression of genes associated with ALS [145] and nabiximols- like combinations of THC and CBD slightly delayed disease progression in SOD1 mice [146] In patients with ALS, PEA slowed reductions in forced vital capacity over time-suggesting that it can improve pulmonary function in this disease and improved the clinical condition of one patient [147,148].

Multiple Sclerosis (MS): TRPV1 regulates cytokine release by activated microglial cells which in turn influences central inflammation in MS [149]. For MS treatment, TRPV1 could be a prime target. Treatment with 2-AG increases the clearance of myelin debris by microglia and OPC differentiation. This results in thickening of the myelin sheath and complete remyelination [150].

In Chronic relapsing experimental allergic encephalomyelitis (CREAE) mice model, CB1 agonists ameliorated tremor and spasticity, whereas antagonists worsened them [151,152]. In CREAE mice, CBD potentiated the anti- spasticity effects of THC [153]. Nabiximols is approved for treatment-resistant spasticity in patients with MS and neuropathic pain that comes along with it in several countries. Clinical practice has confirmed that nabiximols is useful for MS spasticity [154] as an add- on therapy with other anti- spastic agents [155].

Several neurophysiological studies have showed that nabiximols to have a beneficial effect on spinal and cortical excitability. It also has a metaplastic effect on the motor cortex but upper motor neurons are spared. This is the main reason behind its analgesic property, improving sensory responses and evoked potentials [156-159]. However, in an Italian population of patients with MS, around 40% of patients were resistant to the anti- spastic action of the drug [160].

Nabiximols has immunomodulatory effects in MS, raising the possibility that it could be used to alter disease progression [161]. Ultra-micronized PEA has also been tested in patients with MS. The treatment reduced circulating levels of pro-inflammatory cytokines and reduced the adverse effects of interferon-β1a treatment for relapsing–remitting MS [162].

Glioblastoma Multiforme (GBM): CB1 and CB2 agonists decreased the size of tumor and increased survival by reducing angiogenesis in xenograft models with human glioma cells [163-166]. CB2 activation induced differentiation and inhibited gliomagenesis of glioma derived stem- like cells, which express all elements of the endocannabinoid system [167].

Anandamide suppressed proliferation, adhesion, migration and invasion of temozolomide- resistant human U251

gliomablastoma cells [168]. The protective role of TRPV1, the 5′-untranslated regions of human TRPV1 generate a stable transcript that encodes TRPV1v3, a variant of the channel that is very highly expressed in human glioblastoma tissue and stem- like cells and is associated with longer survival of patients [169].

CBD inhibits glioma cell proliferation and migration in vitro; these effects are independent of CB1 but at least partly mediated by CB2 [170]. THC had concentration- dependent effects on xenografts of temozolomide- resistant human glioblastoma T98G cells in mice -low doses stimulated proliferation and high doses inhibited proliferation [171]. CBD was shown to potentiate the anti-proliferative effect of THC, and administration of THC, CBD and temozolomide or radiation greatly increased glioma cell death [172,173].

Finally, CBD increased uptake of chemotherapeutic drugs and caused cytotoxicity in human glioma cells by activating TRPV2 [174], and promoted differentiation while reducing proliferation of glioma-derived stem-like cells by upregulating acute myeloid leukemia 1, a driver of tumor initiation that promotes TRPV2 expression [175].

Sugimoto, et al. investigated the effects of corticosterone on the endocannabinoid system in malignant glioblastoma cells *in vitro*. They found corticosterone inhibited the CBR agonist-induced decrease in cell viability by downregulating the mRNA and protein expressions of CB1 in glioblastoma cells and thereby exhibit anti-tumor properties [176]

Phytanoyl-CoA 2-hydroxylase-interacting protein-like gene PHYHIPL may be a target gene for the treatment and prognosis of GBM, good prognosis accompanied by upregulated PHYHIPL may be the result of retrograde endocannabinoid signaling and the cAMP signaling pathway [177].

Spinal cord injury (SCI): Synthetic cannabinoid WIN55212-2 improves the functional recovery after SCI via inhibition of glyceraldehyde 3-phosphate dehydrogenase (GAPDH/Siah1) cascades in a CB2 receptor dependent manner, indicative of its therapeutic potential for traumatic SCI [178]. A recent systematic review concluded that cannabinoid can be beneficial in reducing pain and spasticity in individuals with SCI, but intricate details like clinical significance and effect magnitude are unclear [186].

A recent animal study by Na, et al. found out CB2R agonist JWH-133 induced exogeneous activation of CB2R improved neurological deficit and blood spinal cord barrier disruption after SCI via inhibition of matrix metallopeptidase 9/toll-like receptors 4 (MMP9/TLR4) expression [187]. A descriptive qualitative study cannabis reduces pain after SCI and increased activities of daily living without having drowsiness, seen with opioids [188].

Post SCI, initiation of nuclear transportation of Siah1 and GADPH happens along with complex formation. This activation complex was inhibited by WIN. Treatment with WIN55212-2 improved survival of neurons in the spinal cord, decreased inflammation and apoptosis thereby improving neurological scores and outcome [189]. In a mice model, CBD was found to decrease heat sensitivity following SCI and this might protect against pathological invasion of T-cell [190].

Na and colleagues showed that activation and upregulation of CB1 and CB2 by remote ischemic preconditioning has protective effect on ischemic-reperfusion injury of spinal cord and maintaining integrity of blood spinal cord barrier [191]. A spanish study by Castellote, et al. showed improvement of spasticity in chronic SCI individuals by Sativex, but side-effects have to borne in mind while using it [192].

Neuropathic pain: CB1 has an important analgesic property which can be an alternative to opioids in treating chronic neuropathic pain [179]. Sharon et al. has reported cannabinoids for otherwise unresponsive pain but care should be taken in frail clinical populations [180]. CB2-specifc compounds, peripherally restricted CB1 compounds, and phytocannabinoids such as CBD are also efficacious in various preclinical models, and may avoid the psychoactive effect associated with centrally acting CB1 receptor agonists, such as Δ9-THC in treatment of chemotherapeutic agent-induced neuropathic pain [181].

A recent paper reported CBD and CBD+THC combination exhibits a predominant anti-inflammatory effect *in vivo*, however, THC alone could not reduce pro-inflammatory or increase anti-inflammatory cytokines [182].

A systemically administered AM404, endocannabinoid reuptake inhibitor, fully activated endocannabinoid system and showed antinociceptive effects. The authors also found out anti-hyperalgesic effects of AM404 was mainly via CB1 and not CB2 and could be promising in treatment of neuropathic pain [183].

A recent literature also reported about the role of GPR55 in the periaqueductal gray of the brainstem responsible in mitigating neuropathic pain. They demonstrated the role of GPR55 in the descending pain control system [184]. On contrary, Canavan, et al. found ineffectiveness of cannabinoids in neuropathic pain [185].

Conclusion

In this article, we have discussed in details about the endocannabinoidome and its role in neurological disorders. Evidence suggests this has excellent potential in treating diseases of CNS. This potential depends on their ability to modulate an endogenous signaling network made of lipid signals i.e, endocannabinoid, their receptor targets, metabolic enzymes, and intracellular/transmembrane/extracellular transporters. Most studies of endocannabinoidome targeting

have been preclinical and more on animal models. More double blind and placebo controlled human studies are required in future for developing new neurotherapeutic agents.

Disclosure

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